REMARKS/ARGUMENTS

After the above amendments, Claims 531-542, 544-548, 550-555 and 558-580 are pending. Support for amended Claims 531, 559, 563, 564 and 566 and for new Claims 577-580 may be found throughout the application, including the claims, as filed.

A. Rejections Under 35 U.S.C. § 112

1. Rejection For Lack Of Enablement

The Examiner has again rejected Claims 531-542, 544-548 and 550-576 under 35 U.S.C. § 112, first paragraph, as lacking enablement for the full scope of the claims. Applicants traverse this rejection for the reasons already of record and for the following additional reasons.

Applicants submitted the Declaration of Dr. David Bar-Or ("Bar-Or Declaration") with their April 20, 2006 response. The Bar-Or Declaration describes the testing of thirty-two peptides covered by the currently pending claims. The peptides of the present invention operate by a common mechanism of metal binding, and all of the thirty-two peptides possess at least one metal-binding site. The peptides were tested in a variety of assays to demonstrate their ability to bind copper and inhibit angiogenesis, and the Bar-Or Declaration provides 70+ working examples which demonstrate the efficacy of the claimed family of metal binding peptides.

Despite this abundance of data, the Examiner contends that the Bar-Or Declaration is insufficient to overcome this rejection because the showing is not commensurate in scope to the claims. The Examiner makes several other generic arguments, but the Examiner only makes one specific criticism of the data. The Examiner observes that "figures D-H, S, and V of the declaration describe peptides with Gly in Position Xaa_2, which is no longer encompassed by the pending claims." In response to this valid criticism, new Claims 577-580 have been added. These new claims cover tripeptides in which Gly may be Xaa_2, so the data referred to by the Examiner are applicable to these new claims.

The Examiner contends that "absent direction/guidance regarding whether the peptide can tolerate the modifications contemplated a non-functional protein may result." The peptides

whose testing is described in the Bar-Or Declaration and in the specification vary by size of the peptide, sequence of the peptide (including different sizes and types of amino acids), hydrophobicity, hydrophilicity and other features. This testing, therefore, demonstrated the efficacy of a wide variety of peptides coming within the scope of the invention, and it is not clear what additional modifications are of concern to the Examiner.

It should be noted that Applicants need not describe all actual embodiments of their invention. See MPEP § 2164.02. The data in the Bar-Or Declaration in combination with that in the specification demonstrate that a wide variety of peptides coming within the scope of the claims are effective in inhibiting angiogenesis. As noted above, Applicants have now provided in excess of 70 working examples and, therefore, submit that there are certainly sufficient working examples of record to support a finding of enablement of the currently pending claims.

It is also the Examiner's position that without "sufficient guidance, determination of having the desired biological characteristics is unpredictable." As described in the application and shown by the data in the Bar-Or application, all of the peptides covered by the claims, including the tested peptides, operate by a common mechanism of metal binding. The Bar-Or Declaration demonstrates the anti-angiogenic activity of at least thirty-two claimed peptides which comprise a wide variety of different types of peptides, thereby providing a substantial portion of the testing of every claimed peptide and further indicating that the results of this significant subsection of the claimed peptides can be extrapolated to the entire family of claimed metal binding peptides. Applicants submit that the data presented in the Bar-Or Declaration confirm and establish that the guidance presented in the specification is sufficient to enable one of skill in the art to make and use the invention as currently claimed without undue experimentation.

For all of the foregoing reasons, Applicants request the Examiner's rejection be withdrawn.

2. Indefiniteness Rejections

The Examiner has rejected Claims 559-562 and 567 on the basis that they are indefinite. For the following reasons, the Examiner is asked to withdraw these rejections.

It is the Examiner's position that Claims 559-562 are improper dependent claims because they fail to further limit the peptide of Claim 531. Although Applicants believe that these claims are proper dependent claims, Applicants have written Claim 559 in independent form in order to expedite prosecution. The scope of Claim 559 is not changed by this amendment.

It is also the Examiner's position that Claim 567 lacks antecedent basis for recitation of "a peptide." It is respectfully submitted that the use of the phrase "a peptide" does not require an antecedent basis in a prior claim since this is the first use of that phrase. This is different than the use of a phrase such as "the peptide" or "said peptide." Applicants do understand, however, that the Examiner is experiencing some confusion because two peptides are being administered and would like some distinction between the two peptides. Accordingly, the above amendments to Claims 563, 564 and 566 specify that a second metal-binding compound is being used in addition to the metal-binding peptide P_1 - P_2. These clarifying amendments do not change the scope of these claims.

B. Rejections Under 35 U.S.C. §§ 102 and 103

1. Rejection Based on Hagiwara et al.

The Examiner has rejected Claims 531, 532, 534-536, 541, 543-545 under 35 U.S.C. § 102(b) being anticipated by JP 62-116565 (Hagiwara et al.). Applicants respectfully traverse this rejection.

Hagiwara et al. teaches the treatment of ulcers with a small group of peptides. Two of these peptides are Asp Ala His Lys and Thr Leu His Arg, as noted by the Examiner. As acknowledged by the Examiner, Hagiwara et al. does not expressly teach the treatment of an angiogenic disease or condition. However, it is the Examiner's position that Hagiwara et al. inherently teaches the treatment of an angiogenic disease or condition with these two peptides.

To establish that Hagiwara et al. inherently teaches Applicants' claimed method, the Examiner must present evidence demonstrating that administration of the Hagiwara et al. peptides to animals to treat ulcers necessarily results in the treatment of an angiogenic disease or condition. The Examiner has not done this. Hagiwara does not teach or suggest the presence of an angiogenic disease or condition in the animals treated with the peptides. Indeed, it is well known that the healing of ulcers requires angiogenesis to occur. See, *e.g.*, Jones et al., *Nat. Med.*, **5**:1418-1423 (1999) and Suzuki et al., *J. Physiol. Pharmacol.*, **49**:515-527 (1998), copies being submitted herewith. Those skilled in the art would not, therefore, recognize, or even suspect, that the Hagiwara et al. peptides would be inhibitors of angiogenesis which could be used to treat an angiogenic disease or condition, as required by the rejected claims.

It is the Examiner's position that: "It is recognized by a person having ordinary skill in the art that structure of the polypeptide necessarily determines the function of the polypeptide." However, this is not the issue with respect to inherency. The issue is whether a person skilled in the art would recognize that administering the peptides taught by Hagiwara et al. in the manner taught by Hagiwara et al. (*i.e.*, to treat ulcers) would necessarily result in the treatment of an angiogenic disease or condition as required by the rejected claims. For the reasons discussed above, they would not.

Finally, the U.S. Patent Statute provides that a new use of a known process, composition of matter or material is patentable. 35 U.S.C. §§ 100 and 101. The rejected claims cover a method of treating an angiogenic disease or condition with a group of peptides P_1 - P_2. Some of the peptides P_1 - P_2 were known prior to Applicants' invention, and some of the peptides P_1 - P_2 are novel peptides. With respect to the known peptides, the claims represent a new use of known compounds, and the U.S. Patent Statute expressly provides that claims of this type are patentable.

For all the foregoing reasons, the Examiner has failed to satisfy the requirements for establishing inherency, and the Examiner is respectfully requested to withdraw this rejection.

2. Rejection Based on Heavner

The Examiner has rejected Claims 531-542, 544-548 and 550-576 on the basis that are anticipated by PCT application WO 95/26744 (Heavner et al.). Applicants respectfully traverses this rejection.

The Examiner does not state any reasons why Heavner et al. anticipates the rejected claims. Therefore, the Examiner has not even established a *prima facie* case of anticipation, and this rejection should be withdrawn for this reason alone.

In any event, Heavner et al. does not anticipate the rejected claims. An anticipating reference must describe, expressly or inherently, all of the elements and limitations of a claimed invention and must enable one of skill in the art to make and use the claimed invention, with the result that the claimed invention is put in possession of the public. Heavner et al. falls far short of these standards.

The rejected claims cover a method of treating an angiogenic disease or condition with a group of metal-binding peptides. Each of the peptides in the group contains from 3-14 amino acids, contains at least one metal-binding site and has His as the third amino acid of the peptide.

Heavner et al. does not describe a group of metal-binding peptides or the use of such a group of peptides for treating an angiogenic disease or condition. Heavner et al. describes a group of peptides which are used to inhibit tumor necrosis factor alpha (TNFα) activity by binding to TNFα to prevent its binding to its p55 and p70 receptors. See, *e.g.*, page 1, lines 3-7, and page 9, lines 1-8, of Heavner et al.

In particular, Heavner et al. describes a group of peptides having SEQ ID NOS: 1-76 which can be used to inhibit TNFα activity in the manner described. The sequences of these peptides seem totally random. No common features or important sequences are described in Heavner et al. which are necessary for the peptides to bind to TNFα, and none can be readily discerned by review of these sequences. There is certainly no requirement for His as the third amino acid, as required for Applicants' metal-binding peptides.

The Examiner refers Applicants to SEQ ID NO: 58 and SEQ ID NO: 76 of Heavner et

al. These two peptides do have His in the third position, as required for the peptides used in the rejected claims. However, SEQ ID NO: 58 and SEQ ID NO: 76 contain 15 amino acids, whereas those peptides used in the rejected claims contain no more than 14 amino acids. Accordingly, SEQ ID NO: 58 and SEQ ID NO: 76 do not come within the scope of the rejected claims.

Heavner et al. does attempt to describe peptides other than SEQ ID NOS: 1-76 for inhibiting TNFα activity by binding to TNFα to prevent its binding to its receptors. Heavner et al. teaches that these other peptides contain from 4 to 25 amino acids and include at least four amino acids of SEQ ID NOS: 1-76 (see, e.g., page 4, lines 5-35, of Heavner et al.), and may contain other amino acids besides those recited in SEQ ID NOS: 1-76 (see page 11, lines 6-7, and page 12, lines 16-17, of Heavner et al.). Again, no common features or important sequences of these peptides are described in Heavner et al. which are necessary for the peptides to inhibit TNFα activity. There is certainly no requirement for His as the third amino acid, as required for the peptides used in the rejected claims. Indeed, the sequences of these Heavner et al. peptides seem totally random.

Quite clearly, Heavner et al. does not provide an enabling description of Applicants' peptides covered by the rejected claims, *i.e.*, Heavner et al. has not put Applicants' group of peptides in the possession of the public. More important, Heavner et al. does not provide an enabling description of Applicants' claimed method of treating an angiogenic disease or condition and has not put Applicants' claimed invention covered by the rejected claims in the possession of the public.

For the foregoing reasons, this rejection should be withdrawn.

3. Rejection Based on Heavner and Shimazawa et al.

The Examiner has rejected Claims 531-542, 544-548 and 550-576 on the basis that they would have been obvious over PCT application WO 95/26744 (Heavner et al.) in view of Shimazawa et al. (*Biol. Pharm. Bull.*, 22(2): 224-226 (1999)). It is the Examiner's position that:

> Heavner et al. describes the method of treating an animal suspected of suffering from a disease or disorder mediated by tumor necrosis factor-α activity comprising the step of administering to said individual a therapeutically effective amount of a peptide . . . which inhibits tumor necrosis factor-α activity, wherein said peptide comprises at least four amino acid residue fragment of a Markush group of peptides . . . . Applicant is referred to SEQ ID NO: 58 and SEQ ID NO: 76, which describes peptides with His in position 3 of the polypeptide sequence.
>
> Shimazawa et al. describes the antiangiogenic activity of tumor necrosis factor-α inhibitors derived from thalidomide (see entire document, particularly 4th and 5th paragraphs, and Table 1).
>
> Thus, it would have been obvious to the person having ordinary skill in the art to treat an angiogenic disease or disorder using the tumor necrosis factor-α inhibitor peptides as described by Heavner et al., because Shimazawa et al. have described the art recognized antiangiogenic activity of tumor necrosis factor-α inhibitors.

Applicants respectfully traverses this rejection.

Shimazawa et al. teaches a group of compounds that are regulators of TNFα production. Some of these compounds also have antiangiogenic activity. However, contrary to the Examiner's contentions, Shimazawa et al. teaches that there is poor correlation between the potencies of the antiangiogenic activity and the TNFα inhibition activity. See the 3rd full paragraph and Table 1 on page 225 of Shimazawa et al. Thus, Shimazawa et al. actually teaches away from a correlation between TNFα inhibition and antiangiogenic activity of compounds, and the teachings of Shimazawa et al. would not have made it obvious that the peptides of Heavner et al. would have antiangiogenic activity.

Further, the compounds of Shimazawa et al. and the peptides of Heavner et al. act to inhibit TNFα activity by two different mechanisms. The Shimazawa et al. compounds act by regulating the production of TNFα (see, *e.g.*, 3rd full paragraph and Table 1 on page 225 of Shimazawa et al.), whereas the peptides of Heavner et al act by binding to TNFα and, thereby, inhibiting the binding of TNFα to its receptors (see page 1, lines 3-7, and page 9, lines 1-8, of Heavner et al.). Thus, even assuming the Examiner is correct about the teachings of Shimazawa et al., there would be no reason to believe that the peptides of Heavner et al. would have activities similar to those of the Shimazawa et al. compounds, since the two groups of

compounds inhibit TNFα activity by entirely different mechanisms.

For the foregoing reasons, this rejection should be withdrawn.

D. Objection To Final Rejection Status and Request For Refund

The Examiner has made the rejections in the present Office Action final on the basis that "Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action." However, the new rejections are rejections that could have been made with respect to the previous claims, since Applicants' amendments presented in their response filed April 20, 2006, were amendments that narrowed the claims. Accordingly, Applicants' amendments did not necessitate the new grounds of rejection, and the rejections in the present Office Action should not have been made final. If the rejections had not improperly been made final, an RCE would not have been needed. For this reason, Applicants request a refund of the RCE fee being submitted herewith.

CONCLUSION

Based upon the foregoing, Applicants believe that all pending claims are in condition for allowance and such disposition is respectfully requested. In the event that a telephone conversation would further prosecution and/or expedite allowance, the Examiner is invited to contact the undersigned.

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Date: January 23, 2007

1: J Physiol Pharmacol. 1998 Dec;49(4):515-27.

Relationship between vascular endothelial growth factor and angiogenesis in spontaneous and indomethacin-delayed healing of acetic acid-induced gastric ulcers in rats.

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Angiogenesis is an important event for gastric ulcer healing. Vascular endothelial growth factor (VEGF) is known to be a potent stimulator of angiogenesis. This study consequently examined VEGF production, VEGF mRNA expression and angiogenesis during the spontaneous and indomethacin-delayed healing of acetic acid-induced ulcers in rats. The production of VEGF, taking place in the normal mucosa, was significantly elevated by ulceration. The mRNA expression of three isoforms of VEGF (VEGF188, VEGF164 and VEGF120) was also detected. Following the increase in VEGF production, angiogenesis was significantly promoted in the ulcer base. VEGF-immunoreactivity was observed in granulocytes, fibroblasts and regenerated epithelial cells. Indomethacin markedly inhibited prostaglandin E2 synthesis in the ulcer base, resulting in the prevention of ulcer healing. Angiogenesis was also significantly inhibited by indomethacin, but neither VEGF production nor VEGF mRNA expression was reduced. Such results suggest that VEGF might play a role in angiogenesis in the spontaneous healing of gastric ulcers in rats. However, the inhibition of angiogenesis in indomethacin-delayed ulcer healing is not explainable on VEGF expression.

PMID: 10069693 [PubMed - indexed for MEDLINE]

1: Nat Med. 1999 Dec;5(12):1418-23.

Comment in:
Nat Med. 1999 Dec;5(12):1348-9.

Inhibition of angiogenesis by nonsteroidal anti-inflammatory drugs: insight into mechanisms and implications for cancer growth and ulcer healing.

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Angiogenesis, the formation of new capillary blood vessels, is essential not only for the growth and metastasis of solid tumors, but also for wound and ulcer healing, because without the restoration of blood flow, oxygen and nutrients cannot be delivered to the healing site. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, indomethacin and ibuprofen are the most widely used drugs for pain, arthritis, cardiovascular diseases and, more recently, the prevention of colon cancer and Alzheimer disease. However, NSAIDs produce gastroduodenal ulcers in about 25% of users (often with bleeding and/or perforations) and delay ulcer healing, presumably by blocking prostaglandin synthesis from cyclooxygenase (COX)-1 and COX-2 (ref. 10). The hypothesis that the gastrointestinal side effects of NSAIDs result from inhibition of COX-1, but not COX-2 (ref. 11), prompted the development of NSAIDs that selectively inhibit only COX-2 (such as celecoxib and rofecoxib). Our study demonstrates that both selective and nonselective NSAIDs inhibit angiogenesis through direct effects on endothelial cells. We also show that this action involves inhibition of mitogen-activated protein (MAP) kinase (ERK2) activity, interference with ERK nuclear translocation, is independent of protein kinase C and has prostaglandin-dependent and prostaglandin-independent components. Finally, we show that both COX-1 and COX-2 are important for the regulation of angiogenesis. These findings challenge the premise that selective COX-2 inhibitors will not affect the gastrointestinal tract and ulcer/wound healing.

PMID: 10581086 [PubMed - indexed for MEDLINE]